

65. (Reiterated) The nucleic acid sequence of claim 64, wherein the continuous stretch occurs in a nucleic acid sequence which is selected from a group of sequences consisting of a sequence of a pre-pro-protein; a sequence of a pro-protein; a sequence of a mature protein; a "pre" sequence of a pre-pro-protein; a "pre-pro" sequence of a pre-pro-protein; a "pro" sequence of a pre-pro or a pro-protein; or a portion of any of the aforementioned sequences.

66. (Reiterated) The nucleic acid sequence of claim 64, wherein the continuous stretch comprises at least 200 common codons.

67. (Reiterated) The nucleic acid of claim 64, wherein the number of non-common or less-common codons remaining is between one and 15.

68. (Reiterated) The nucleic acid of claim 64, wherein all of the non-common and less-common codons of the synthetic nucleic acid sequence encoding a protein have been replaced with common codons.

69. **(Twice Amended)** A synthetic nucleic acid sequence which encodes a human protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence comprises a continuous stretch of common codons, which continuous stretch includes at least 60% or more of the codons in the synthetic nucleic acid sequence, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

70. (Reiterated) The nucleic acid of claim 69, wherein all of the non-common and less-common codons of the synthetic nucleic acid sequence encoding a protein have been replaced with common codons.

71. (Reiterated) The nucleic acid sequence of claim 69, wherein the continuous stretch occurs in a nucleic acid sequence which is selected from a group of sequences consisting of a sequence of a pre-pro-protein; a sequence of a pro-protein; a sequence of a mature protein; a "pre" sequence of a pre-pro-protein; a "pre-pro" sequence of a pre-pro-protein; a "pro" sequence of a pre-pro or a pro-protein; or a portion of any of the aforementioned sequences.

72. (Reiterated) The nucleic acid of claim 69, wherein the number of non-common or less-common codons replaced or remaining is between one and 15.

C³ 73. (Twice Amended) A synthetic nucleic acid sequence which encodes a human protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and wherein at least 98% or more of the codons in the sequence encoding the protein are common codons and wherein the protein is at least 90 amino acid residues in length, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

74. (Reiterated) The nucleic acid sequence of claim 73, wherein the continuous stretch occurs in a nucleic acid sequence which is selected from a group of sequences consisting of a sequence of a pre-pro-protein; a sequence of a pro-protein; a sequence of a mature protein; a "pre" sequence of a pre-pro-protein; a "pre-pro" sequence of a pre-pro-protein; a "pro" sequence of a pre-pro or a pro-protein; or a portion of any of the aforementioned sequences.

75. (Reiterated) The nucleic acid of claim 73, wherein the number of non-common or less-common codons replaced or remaining is between one and 15.

76. (Reiterated) The nucleic acid of claim 73, wherein the non-common and less-common codons, taken together, replaced or remaining, are equal or less than 2% of the codons in the synthetic nucleic acid sequence.

77. (Reiterated) The nucleic acid of claim 73, wherein all of the non-common and less-common codons of the synthetic nucleic acid sequence encoding a protein have been replaced with common codons.

78. (Reiterated) The nucleic acid of claim 73, wherein the nucleic acid sequence encodes a protein of at least 105 amino acid residues in length.

79. (Reiterated) The nucleic acid of claim 73, wherein at least 99% of the codons in the synthetic nucleic acid sequence are common codons.

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81. **(Twice Amended)** A synthetic nucleic acid sequence which encodes human Factor VIII or a functional portion thereof, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of at least 150 codons all of which are common codons, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

82. (Reiterated) The synthetic nucleic acid sequence of claim 81 where the factor VIII protein has one or more of the following characteristics:

- a) the B domain is deleted (beta domain deleted (BDD) factor VIII);
- b) it has a recognition site for an intracellular protease of the PACE/furin class; or
- c) it is expressed in a non-transformed cell.

83. (Reiterated) The synthetic nucleic acid sequence of claim 81, wherein the number of non-common or less-common codons replaced or remaining is between one and 15.

84. (Reiterated) The synthetic nucleic acid sequence of claim 81, wherein all non-common and less-common codons are replaced with common codons.

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85. (Twice Amended) A synthetic nucleic acid sequence which encodes human Factor VIII or a functional portion thereof, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least 60% of the codons of the synthetic nucleic acid sequence, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

86. (Reiterated) The synthetic nucleic acid sequence of claim 85 where the factor VIII protein has one or more of the following characteristics:

- a) the B domain is deleted (BDD factor VIII);
- b) it has a recognition site for an intracellular protease of the PACE/furin class;

or

- c) it is expressed in a non-transformed cell.

87. (Reiterated) The synthetic nucleic acid sequence of claim 85, wherein the number of non- common or less- common codons replaced or remaining is between one and 15.

88. (Reiterated) The synthetic nucleic acid sequence of claim 85, wherein all non-common and less-common codons are replaced with common codons.

89. (**Twice Amended**) A synthetic nucleic acid sequence which encodes human Factor VIII or a functional portion thereof, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein at least 98% or more of the codons in the sequence encoding the Factor VIII are common codons and the Factor VIII is at least 90 amino acid residues in length, and wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

90. (**Amended**) The synthetic nucleic acid sequence of claim 89 where the factor VIII protein has one or more of the following characteristics:

- a) the B domain is deleted (BDD factor VIII);
- b) it has a recognition site for an intracellular protease of the PACE/furin class;

and

- c) it is expressed in a non-transformed cell.

91. (Reiterated) The synthetic nucleic acid sequence of claim 89, wherein the number of non-common or less-common codons replaced or remaining is between one and 15.

92. (Reiterated) The synthetic nucleic acid sequence of claim 89, wherein the number of non-common or less-common codons replaced or remaining, taken together, are equal or less than 2% of the codons in the synthetic nucleic acid sequence.

93. (Reiterated) The synthetic nucleic acid sequence of claim 89, wherein all non-common and less-common codons are replaced with common codons.

94. (Reiterated) The synthetic nucleic acid sequence of claim 89, wherein at least 99% of the codons in the synthetic nucleic acid sequence are common codons.

96. (Reiterated) The synthetic nucleic acid sequence of claim 89, wherein all of the codons are replaced with common codons.

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97. **(Twice Amended)** A synthetic nucleic acid sequence which encodes human Factor IX, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of at least 150 codons all of which are common codons, and wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

98. **(Amended)** The synthetic nucleic acid sequence of claim 97, wherein the Factor IX protein has one or more of the following characteristics:

- a) it has a PACE/furin site at a pro-peptide mature protein junction; and
- b) is expressed in a non-transformed cell.

99. **(Reiterated)** The synthetic nucleic acid sequence of claim 97, wherein the number of non- common or less- common codons replaced or remaining is between one and 15.

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100. **(Twice Amended)** A synthetic nucleic acid sequence which encodes human Factor IX, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least 60% of the codons of the synthetic nucleic acid sequence, and wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

101. **(Reiterated)** The synthetic nucleic acid sequence of claim 100, wherein the number of non- common or less- common codons replaced or remaining is between one and 15.

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102. **(Amended)** The synthetic nucleic acid sequence of claim 100, wherein the factor IX protein has one or more of the following characteristics:

- a) it has a PACE/furin site at a pro-peptide mature protein junction; and
- b) is expressed in a non-transformed cell.

103. **(Twice Amended)** A synthetic nucleic acid sequence which encodes human Factor IX, wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon and wherein at least 98% or more of the codons in the sequence encoding the Factor IX are common codons and the Factor IX is at least 90 amino acid residues in length, and wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

104. **(Amended)** The synthetic nucleic acid sequence of claim 103, wherein the factor IX protein has one or more of the following characteristics:

- a) it has a PACE/furin site at a pro-peptide mature protein junction; and
 - b) is expressed in a non-transformed cell.
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105. **(Reiterated)** The synthetic nucleic acid sequence of claim 103, wherein the number of non- common or less- common codons replaced or remaining is between one and 15

106. **(Reiterated)** The synthetic nucleic acid sequence of claim 103, wherein the number of non- common or less- common codons replaced or remaining, taken together, are equal or less than 2% of the codons in the synthetic nucleic acid sequence.

107. **(Reiterated)** The synthetic nucleic acid sequence of claim 103, wherein all non-common and less-common codons are replaced with common codons.

108. **(Reiterated)** The synthetic nucleic acid sequence of claim 103, wherein at least 99% of the codons in the synthetic nucleic acid sequence are common codons.

110. (Reiterated) The synthetic nucleic acid sequence of claim 103, wherein all of the codons are replaced with common codons.

111. (Reiterated) A vector comprising the synthetic nucleic acid sequence of claim 64, 69, 73, 81, 85, 89, 97, 100, or 103.

112. (Reiterated) A cell comprising the nucleic acid sequence of claim 64, 69, 73, 81, 85, 89, 97, 100, or 103.

113. **(Twice Amended)** A synthetic nucleic acid sequence which encodes a human protein wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, and having the following properties:

(i) the synthetic nucleic acid sequence comprises a continuous stretch of at least 150 codons all of which are common codons;

C¹⁰ (ii) the synthetic nucleic acid sequence comprises a continuous stretch of common codons, which continuous stretch includes at least 60% or more of the codons in the synthetic nucleic acid sequence; and

(iii) wherein at least 98% or more of the codons in the sequence encoding the protein are common codons and wherein the protein is at least 90 amino acid residues in length.

114. **(Twice Amended)** A method for preparing a synthetic nucleic acid sequence which is at least 90 codons in length, comprising:

identifying a non-common codon and a less-common codon in a non-optimized gene sequence which encodes a human protein and is at least 90 codons in length; and

replacing at least 98% of the non-common and less-common codons with a common codon encoding the same amino acid residue as the replaced codon, wherein by a

common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1.

115. (Reiterated) The method of claim 114, wherein at least 99% of the non-common and less-common codons are replaced with a common codon encoding the same amino acid residue as the replaced codon.

116. (**Twice Amended**) A method for making a nucleic acid sequence which directs the synthesis of an optimized message of a human protein of at least 90 amino acids comprising:

C11 synthesizing at least two fragments of a nucleic acid sequence, wherein the two fragments encode adjoining portions of a human protein of at least 90 amino acids and wherein both fragments are mRNA optimized; and

joining the two fragments such that a non-common codon is not created at a junction point, thereby making the mRNA optimized nucleic acid sequence.

117. (Reiterated) The method of claim 116, wherein 98% of the codons in the synthetic nucleic acid sequence are common codons.

118. (Reiterated) The method of claim 116, wherein each fragment is at least 30 codons in length.

C12 119. (**Twice Amended**) A method for preparing a synthetic nucleic acid sequence encoding a human protein which is at least 90 amino acid residues in length, comprising identifying non-common codon and less-common codons in the non-optimized nucleic acid sequence encoding a protein of at least 90 amino acid residues in length and replacing at least 98% or more of the non-common and less-common codons of the nucleic acid sequence encoding the protein with a common codon encoding the same amino acid residue as the replaced codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, thereby

preparing a synthetic nucleic acid sequence encoding a human protein which is at least 90 amino acid residues in length.

120. **(Twice Amended)** A primary or secondary mammalian cell having an exogenous synthetic nucleic acid sequence which encodes a human protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, and wherein the synthetic nucleic acid has a continuous stretch of at least 150 codons all of which are common codons; is at least 80 base pairs in length; and is free of unique restriction endonuclease sites in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the human protein or polypeptide product.

122. (Reiterated) The primary or secondary cell of claim 120, wherein the exogenous synthetic nucleic acid sequence is stably integrated into its genome.

123. (Reiterated) The primary or secondary cell of claim 120, wherein the exogenous synthetic nucleic acid is present in the cell in an episome.

124. (Reiterated) The primary or secondary cell of claim 120, wherein the DNA sequence sufficient for expression of the exogenous synthetic nucleic acid is of non-viral origin.

125. **(Twice Amended)** A primary or secondary mammalian cell having an exogenous synthetic nucleic acid sequence which encodes a human protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding

the same amino acid residue as the non-common or less-common codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, and wherein the synthetic nucleic acid has a continuous stretch of common codons which comprise at least 60% of the codons of the synthetic nucleic acid sequence, is at least 80 base pairs in length and is free of unique restriction endonuclease sites in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;

the primary or secondary cell capable of expressing the human protein or polypeptide product.

127. (Reiterated) The primary or secondary cell of claim 125, wherein the exogenous synthetic nucleic acid sequence is stably integrated into its genome.

128. (Reiterated) The primary or secondary cell of claim 125, wherein the exogenous synthetic nucleic acid is present in the cell in an episome.

129. (Reiterated) The primary or secondary cell of claim 125, wherein the DNA sequence sufficient for expression of the exogenous synthetic nucleic acid is of non-viral origin.

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130. (Twice Amended) A primary or secondary mammalian cell having an exogenous synthetic nucleic acid sequence which encodes a human protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, and wherein at least 98% or more of the codons in the sequence encoding the protein are common codons and the protein is at least 90 amino acids in length; the nucleic acid sequence is at least 80 base pairs in length and is free of unique restriction endonuclease sites in the message optimized sequence; and has

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;
the primary or secondary cell capable of expressing the human protein or polypeptide product.

132. (Reiterated) The primary or secondary cell of claim 130, wherein the exogenous synthetic nucleic acid sequence is stably integrated into its genome.

133. (Reiterated) The primary or secondary cell of claim 130, wherein the exogenous synthetic nucleic acid is present in the cell in an episome.

134. (Reiterated) The primary or secondary cell of claim 130, wherein the DNA sequence sufficient for expression of the exogenous synthetic nucleic acid is of non-viral origin.

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135. (**Twice Amended**) A primary or secondary mammalian cell having an exogenous synthetic nucleic acid sequence which encodes a human protein or a polypeptide wherein at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, wherein by a common codon is meant the most common codon encoding each particular amino acid residue in highly expressed human genes as shown in Table 1, and wherein the synthetic nucleic acid has the following properties: it has a continuous stretch of at least 150 codons all of which are common codons; it has a continuous stretch of common codons which comprise at least 60% of the codons of the synthetic nucleic acid sequence; at least 98% or more of the codons in the sequence encoding the protein are common codons and the protein is at least 90 amino acids in length; it is at least 80 base pairs in length and which is free of unique restriction endonuclease sites in the message optimized sequence; and

DNA sequences, sufficient for expression of the exogenous synthetic DNA in the transfected primary or secondary cell;
the primary or secondary cell capable of expressing the human protein or polypeptide product.
